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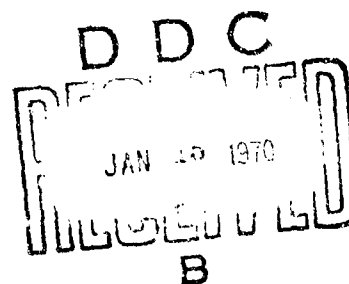
EATR 4328

OBSERVATIONS ON CERTAIN
ENDOCRINOLOGICAL RESPONSES OF THE HAMSTER

by

Paul F. Robinson

January 1970



DEPARTMENT OF THE ARMY
EDGEWOOD ARSENAL
Research Laboratories
Medical Research Laboratory
Edgewood Arsenal, Maryland 21010

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Task 1TC61101A91A15

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FOREWORD

The work described in this report was authorized under Task 1T061101A91A15, In-House Laboratory Independent Research - Edgewood (U). The experiments were performed between July 1966 and August 1967.

In conducting the research described in this report, the investigator adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

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DIGEST

Some endocrinological responses of the hamster are similar to those of the albino rat; however, there are important differences.

In the hamster, as in the rat, chemical thyroidectomy effects little or no significant change in the ascorbic acid content of the pituitary gland.

The hamster, unlike the rat, shows no significant change in the ascorbic acid content of the adrenal, pituitary, hypothalamus, cerebrum, or liver for a period of up to 15 days following ovariectomy.

l-Alanine does not exert a gluconeogenic effect upon the liver of fasted hamsters of either sex, whereas it rapidly replenishes the glycogen stores of fasted rats. Following adrenalectomy, neither hamsters nor rats show any increase in liver glycogen after having ingested *l*-alanine.

Corticosterone is unable to stimulate repletion of liver glycogen in either the normal or adrenalectomized hamster, whereas the closely allied steroid cortisol is very efficacious under these conditions in the rat.

CONTENTS

| | <u>Page</u> |
|---|-------------|
| I. INTRODUCTION | 7 |
| II. ASCORBIC ACID CONTENT OF THE HAMSTER PITUITARY FOLLOWING CHEMICAL THYROIDECTOMY | 8 |
| A. Methods | 8 |
| B. Results and Discussion | 9 |
| III. ASCORBIC ACID CONTENT OF NERVOUS AND ENDOCRINE TISSUE OF THE HAMSTER FOLLOWING OVARIECTOMY | 10 |
| A. Methods | 11 |
| B. Results and Discussion | 11 |
| IV. EFFECT OF <i>l</i> -ALANINE AND CORTICOSTERONE ON THE LIVER GLYCOGEN AND ADRENAL ASCORBIC ACID OF NORMAL AND ADRENALECTOMIZED HAMSTERS | 14 |
| A. Methods | 14 |
| B. Results | 15 |
| V. CONCLUSIONS | 17 |
| LITERATURE CITED | 19 |
| DISTRIBUTION LIST | 21 |

LIST OF TABLES

| <u>Table</u> | | <u>Page</u> |
|--------------|--|-------------|
| I. | The Ascorbic Acid Content of the Pituitaries of Hamsters Fed Thiourea | 9 |
| II. | Ascorbic Acid Content of Nervous and Endocrine Tissue after Ovariectomy of the Hamster | 12 |
| III. | Ascorbic Acid Content of the Hamster Pituitary after Ovariectomy | 13 |
| IV. | Effect of <i>l</i> -Alanine on Liver Glycogen and Adrenal Ascorbic Acid of Fasted Hamsters | 15 |
| V. | Effect of <i>l</i> -Alanine on the Liver Glycogen of Normal and Adrenalectomized Fasted Hamsters | 16 |
| VI. | Effect of Corticosterone on the Liver Glycogen of Normal and Adrenalectomized Fasted Hamsters . . . | 17 |

OBSERVATIONS ON CERTAIN ENDOCRINOLOGICAL RESPONSES OF THE HAMSTER

I. INTRODUCTION.

The golden hamster has been used widely as a laboratory animal for about 30 years in investigations of parasitic, viral, and neoplastic diseases. It has also been used many times in studies related to cariogenesis in teeth. The hamster has been employed to a much lesser extent in pharmacological studies where, aside from a relatively few peculiar responses, this species reacts to chemicals in much the same manner as the white rat.¹ Very little, however, is known concerning the endocrine system of the hamster since there has never been a systematic investigation of this aspect of the hamster's physiology. It was primarily for this reason that the following studies were carried out. Secondly, the aim of the research to be described was to determine, if possible, what unique endocrinological characteristics the hamster might possess that would suit it for certain types of experimentation useful in these laboratories.

The net impression to be gained after examining the results of this effort is that this species is remarkably refractory to the usual stimuli. However, this could conceivably be of considerable value in certain situations where stability of the adrenal-pituitary relationship would be of prime importance, for instance in experiments involving stress such as heat and cold. The history of the laboratory utilization of the less familiar species, which often possess special attributes, is too well known and commented upon to need further elaboration.²

The greatest need at the moment, it would seem, is for a broad program of investigation to be carried out in the area of hamster endocrinology. This would not only identify similarities and differences, but would uncover mechanisms of action. Equipped with this knowledge, the investigator could well have a potent tool with which to attack problems of peculiar interest to these laboratories, especially those of a pharmacological nature. It is most likely that, in the divergency of a species response, clues to fundamental biological phenomena and therapeutic approaches may be disclosed.

II. ASCORBIC ACID CONTENT OF THE HAMSTER PITUITARY FOLLOWING CHEMICAL THYROIDECTOMY.

There can be little doubt that ascorbic acid plays a regulatory role of some sort in the hypothalamo-hypophyseal servo system. The precise nature of this role has never been delineated, even though it has been 25 years since Sayers et al. first described the relationship between adrenocorticotrophic hormone (ACTH) and adrenal ascorbic acid.^{3, 4}

The adenohypophysis is second only to the adrenals in ascorbic acid content. Changes in its content are usually observed whenever the organism is subjected to a stress or when there is a deficiency of the hormones of the peripheral endocrine glands.^{5, 6} However, Schreiber and Kmentova reported that there was no significant alteration of the ascorbic acid content of the rat adenohypophysis after thyroidectomy, a state which presumably should induce a maximum hypersecretion of thyroid-stimulating hormone (TSH).⁷

Since no similar observations had been made on the hamster, a species known to respond atypically in many cases to endocrinological stimuli, the following study was initiated, wherein hamsters were chemically thyroidectomized with thiourea and the adenohypophysis was examined for possible alterations in its ascorbic acid content.

Chemical thyroidectomy is to be preferred to surgical ablation of the organ because it leaves little chance of thyroid fragments being left behind to regenerate. Also, there is probably less trauma involved, consequently, less change in the general condition of the animal.

Thiourea exerts its antithyroid activity by blocking the iodination of tyrosine. Hence, thyroxine cannot be synthesized and the level of circulating thyroxine drops. This elicits an augmented output of TSH by the anterior pituitary, and the latter hormone causes hypertrophy, hyperplasia, and perhaps most important of all, loss of colloid from the thyroid gland.

A. Methods.

The experiments were carried out on female hamsters weighing from 120 to 150 grams. The hamsters were maintained at a

room temperature of $25 \pm 2^{\circ}\text{C}$ and fed a diet of commercial pellets. Water was available at all times. The drinking water of the treated groups contained 0.2% thiourea. After 21 to 24 days of treatment, both the control and experimental groups were killed by decapitation and the pituitary and adrenals were removed from each animal and weighed. The pituitaries were homogenized in 4% trichloroacetic acid and the ascorbic acid content of the filtrate was measured by the method of Roe and Kuether.⁸

B. Results and Discussion.

Thiourea feeding seems to cause little or no significant change in the ascorbic acid content of the pituitary (table I). This seems to confirm the observations made on thyroidectomized rats by Schreiber and Kmentová.⁷ They also found that the weight of the hypophyses increases and the weight of the adrenals decreases after chemical thyroidectomy of the rat.⁹ There is some suggestion of this trend in the data presented in table I.

Table I. The Ascorbic Acid Content of the Pituitaries of Hamsters Fed Thiourea

| Group | Days fed thiourea | Pituitary weight | Adrenal weight | Pituitary ascorbic acid |
|-------------------|-------------------|------------------|----------------|-------------------------|
| | | mg | mg | mg/100 mg |
| Control (10) | - | 4.20 ± 0.19 | - | 0.189 ± 0.019 |
| Experimental (8) | 21 | 4.26 ± 0.15 | - | 0.222 ± 0.008 |
| Control (9) | - | 3.58 ± 0.28 | 2.8 ± 0.56 | 0.188 ± 0.011 |
| Experimental (15) | 24 | 3.79 ± 0.13 | 3.8 ± 0.28 | 0.188 ± 0.011 |

Values are means \pm standard errors. The numbers in parentheses indicate the number of hamsters used

We were not able to make a histological examination of the thyroids of our thiourea-treated hamsters and thus evaluate the damage caused by the goitrogen. However, Harris et al., in their comparative study of the action of alloxan, senecionine, sulfadiazine, and thiouracil on several species, did examine the histological changes that took place in the thyroid and concluded that unquestionably the goitrogenic action of thiouracil on the hamster was the same as that on the mouse, rat, guinea pig, rabbit, and dog, although somewhat less intense.¹⁰ The intensity may have been lessened by the fact that Harris incorporated the drug in the diet of his animals to the extent of 0.1%. We fed the drug by means of a 0.2% solution in their drinking water. This concentration did not seem to diminish the daily water intake of the animals.

III. ASCORBIC ACID CONTENT OF NERVOUS AND ENDOCRINE TISSUE OF THE HAMSTER FOLLOWING OVARIECTOMY.

Although the ascorbic acid content of the hypothalamic area of the brain is only about 10% of that of the adrenal, nevertheless it is present in readily measurable quantities. The cerebral hemispheres also contain this vitamin, and its concentration is about 50% greater than in the hypothalamus. In neither organ is its functional significance at all clear, although speculation regarding its role has not been lacking. Imoto¹¹ considered that the reducing properties of ascorbic acid were of great importance in the regulation of neurosecretory activity.

One approach to the study of this problem was that undertaken by Schreiber and Kmentová⁷ who demonstrated that changes in the ascorbic acid content of the hypothalamus and its associated structures occurred in both male and female rats after castration. Presumably the deficiency of the gonadal hormone stimulated the hypothalamic servomechanism, a part of whose function is the biosynthesis and secretion of hypophysiotropic factors. The resulting elevation of the biosynthetic effort very possibly was the causative factor in the observed depletion of ascorbic acid.

This study on hamsters was designed to answer the question of whether peripheral glandectomy would deplete ascorbic acid stores in this species which has previously been shown to respond in a somewhat equivocal fashion to endocrinological stress.¹²

A. Methods.

One hundred and four female hamsters ranging in weight from 75 to 140 grams were used. The ovariectomies were performed while the animals were under light ether anesthesia. Before and after the operation, the animals were maintained on a diet of commercial pellets. Water was available at all times. At appropriate intervals after ovariectomy, as indicated below, groups of the prepared hamsters along with a similar number of controls were anesthetized and killed by exsanguination. The brain was exposed and a block of tissue containing the median eminence and hypothalamic area (approximately 70 mg) was excised. Blocks were also taken from the cerebrum and the liver. The pituitary and one adrenal gland were also removed for analysis. After being weighed, the tissues were homogenized in 4% trichloroacetic acid and the ascorbic acid content of the filtrate was measured by the method of Roe and Kuether.⁸

B. Results and Discussion.

Table II summarizes the results obtained from the analysis of samples from six organs taken on the fourth and tenth days following ovariectomy. It is apparent that no change whatever occurred in the ascorbic acid content of the hypothalamus, cerebrum, and liver.

The pituitary ascorbic acid values seemed to decline slightly 10 days after the operation, and the level of ascorbic acid in the adrenal would appear to increase somewhat 4 days postoperatively. These changes, however, were not statistically significant.

A second series of experiments was carried out over a longer period of time, in which the ascorbic acid content of the pituitary alone was considered. Table III demonstrates that up to 15 days after ovariectomy there was no significant difference between the means of the control and experimental groups.

The several authors who have investigated the three-way relationship that evidently exists between the ascorbic acid content of certain portions of the central nervous system, the level of this compound in the endocrine organs, and the secretory activity of the steroid-producing glands have by no means reached unanimity. Schreiber and Kmentová found that in the castrated rat of either sex a significant drop occurred in

Table II. Ascorbic Acid Content of Nervous and Endocrine Tissue
after Ovariectomy of the Hamster

| Days after ovariectomy | Ascorbic acid mg/100 mg | | | | | |
|---------------------------|----------------------------|---------------|---------------|---------------|---------------|---------------|
| | Ovary | Adrenal | Pituitary | Hypothalamus | Cerebrum | Liver |
| Control (%) | 0.518 ± 0.202 | 0.167 ± 0.009 | 0.161 ± 0.010 | 0.028 ± 0.011 | 0.037 ± 0.001 | 0.028 ± 0.001 |
| 3-4 (8) | - | 0.197 ± 0.013 | 0.172 ± 0.015 | 0.028 ± 0.001 | 0.037 ± 0.001 | 0.027 ± 0.001 |
| 10 (8) | - | 0.168 ± 0.015 | 0.144 ± 0.025 | 0.027 ± 0.012 | 0.036 ± 0.001 | 0.025 ± 0.001 |

Values are means ± standard errors. The numbers in parentheses indicate the number of hamsters used.

Table III. Ascorbic Acid Content of the Hamster Pituitary after Ovariectomy

| Days after ovariectomy | Pituitary ascorbic acid | |
|------------------------|-------------------------|-------------------|
| | Control | Experimental |
| | mg/100 mg | |
| 3-4 (17) | 0.161 \pm 0.010 | 0.172 \pm 0.015 |
| 7 (14) | 0.125 \pm 0.007 | 0.115 \pm 0.017 |
| 10 (27) | 0.156 \pm 0.009 | 0.166 \pm 0.009 |
| 15 (21) | 0.132 \pm 0.017 | 0.099 \pm 0.016 |

Values are means \pm standard errors. The numbers in parentheses indicate the number of hamsters used.

the ascorbic acid level of the hypothalamus in half of the test animals; the other half failed to respond.⁷ They felt that this lack of response may have been due to their not always having extirpated the proper area of the hypothalamus or alternatively that unknown substances in the tissue may have interfered with the biochemical method used for analysis. An earlier investigator, Imoto, utilizing histochemical techniques, demonstrated a pronounced drop in hypothalamic ascorbic acid following castration of the female rat.¹¹ Kimura observed a moderate but temporary decrease in this substance in the adenohypophysis of the male rat after castration.⁵

Experimental evidence from these laboratories tends to confirm the work of Kimura.⁵ The ascorbic acid level in the pituitary of 6- to 7-week-old rats that had been castrated at birth was significantly lower than that of 6-week-old animals in the control group. In rats that were 16 weeks old, the pituitary ascorbic acid concentration was the same in both the castrated and control groups.*

* Robinson, P. F. Unpublished data.

IV. EFFECT OF L-ALANINE AND CORTICOSTERONE ON THE LIVER GLYCOGEN AND ADRENAL ASCORBIC ACID OF NORMAL AND ADRENALECTOMIZED HAMSTERS.

It has been amply demonstrated that the adrenocortical hormones profoundly affect carbohydrate metabolism in the mammal. Long showed that exogenous adrenocortical hormones increase the stores of carbohydrate¹³ by inducing gluconeogenesis. Haynes and Okuno,^{14, 15} and later Eisenstein et al.¹⁶ in a series of experiments in vitro found that adrenal steroids stimulate carbohydrate synthesis from alanine. Zaki,¹⁷ in order to determine whether the foregoing studies were valid when performed in vivo, measured the liver glycogen and adrenal ascorbic acid of both normal and adrenalectomized albino rats before and after ingestion of alanine. He found that the liver glycogen stores of fasted rats were considerably higher in alanine-fed animals than in the control animals, whereas the ascorbic acid content of the adrenal gland declined somewhat. The maximum effect in regard to both ascorbic acid and glycogen was reached about 6 hours after the animals received alanine.

Similar experiments carried out on both normal and adrenalectomized hamsters in these laboratories produced somewhat different results.

A. Methods.

Adult hamsters, both male and female, weighing between 50 and 60 grams were employed in all but one set of experiments, in which a somewhat heavier group was used. The animals were fasted for 24 hours prior to treatment, but water was supplied ad libitum. The amino acid L-alanine, 400 mg/100 gm body weight, was dissolved in water and administered by stomach tube. Four to six hours after the ingestion of alanine, the animals were killed by decapitation and the liver glycogen was determined by the method of Montgomery¹⁸ and the adrenal ascorbic acid was determined by the method of Roe and Kuether.⁸ The adrenalectomized hamsters were used 6 days after bilateral extirpation of the glands. After the operation, they were maintained on 1% saline. The animals receiving corticosterone were given 3 mg of the steroid in a divided dose administered intraperitoneally every 2 hours for a total of four injections. The animals were killed 2 hours after the last injection.

B. Results.

Table IV summarizes the results obtained 4 hours after the ingestion of *l*-alanine. Despite the ingestion of alanine, the liver glycogen declined appreciably. The adrenal ascorbic acid was not significantly affected. In a later experiment in which technical difficulties interfered with the accurate measurement of the liver glycogen, the adrenal ascorbic acid content again showed no significant alteration 6 hours after the ingestion of *l*-alanine.

If adrenalectomized hamsters are treated with *l*-alanine by the schedule indicated above, there is no significant increase in the very small amount of glycogen remaining in their liver tissue (table V). This is in accordance with the finding of Zaki, who used rats.¹⁷

It is apparent that *l*-alanine does not exert a gluconeogenic effect upon the liver of fasted hamsters. It also seems reasonable to assume that neither does it stimulate the adrenal cortex since the ascorbic acid content of the adrenal remains unchanged 6 hours after the administration of alanine.

Table IV. Effect of *l*-Alanine on Liver Glycogen and Adrenal Ascorbic Acid of Fasted Hamsters

| Time after ingestion of alanine | Liver glycogen | | Adrenal ascorbic acid | |
|---------------------------------------|------------------|--------------|-----------------------|--------------|
| | Control (10) | Alanine (10) | Control (10) | Alanine (10) |
| hr | mg/100 mg wet wt | | mg/100 mg wet wt | |
| 0 | 2.77 ± 0.52 | - | 2.02 ± 0.01 | - |
| 4 | - | 1.70 ± 0.16 | - | 2.16 ± 0.20 |
| 6 | - | - | 1.92 ± 0.05 | 1.76 ± 0.10 |

Values are means ± standard errors. The numbers in parentheses indicate the number of hamsters used.

Table V. Effect of *l*-Alanine on the Liver Glycogen of Normal and Adrenalectomized Fasted Hamsters

| Treatment | Liver glycogen | |
|---|-----------------|-------------------|
| | Normal | Adrenalectomized |
| | mg/gm | |
| Control - nonfasted (8) | 4.73 \pm 0.68 | - |
| 24-hour fasted (8) | 0.84 \pm 0.02 | 0.043 \pm 0.003 |
| 6 hours after feeding <i>l</i> -alanine | 0.81 \pm 0.01 | 0.052 \pm 0.01 |

Values are means \pm standard errors. The numbers in parentheses indicate the number of hamsters used.

The failure of alanine to be converted to glycogen by the hamster liver tempts speculation that the deamination mechanism whereby alanine is converted to pyruvic acid may be different in the hamster than in other rodents.

The data shown in table VI demonstrate that corticosterone is unable to stimulate repletion of liver glycogen in either the normal or adrenalectomized fasted hamster. This is in contrast to the action of cortisol in the rat. Cortisol administered to the fasted normal or adrenalectomized rat elevates the glycogen to a level approximately three times as high as the control value. Corticosterone, whether administered to a normal fasting hamster or to one that is adrenalectomized, fails to alter significantly the level of glycogen stores.

Oliver and Péron¹⁹ assert that the adrenal of the hamster, unlike that of most rodents, does not produce detectable amounts of corticosterone. Their work is based upon the measurement of the steroid content of hamster serum by chromatographic techniques rather than the less specific chemical methods of other authors.

Table VI. Effect of Corticosterone on the Liver Glycogen of Normal and Adrenalectomized Fasted Hamsters

| Liver glycogen | | | |
|---------------------|-------------------------|----------------------|-----------------------------------|
| Normal | Normal + corticosterone | Adrenalectomized | Adrenalectomized + corticosterone |
| mg/gm | | | |
| 1.76 \pm 0.13 (9) | - | 0.63 \pm 0.20 (10) | - |
| 3.59 \pm 0.14 (8) | - | - | 1.69 \pm 0.39 (6) |
| 3.30 \pm 0.39 (8) | 2.6 \pm 0.51 (6) | - | - |

Values are means \pm standard errors. The numbers in parentheses indicate the number of hamsters used.

Since it has been amply demonstrated in the past that adrenal corticoids promote gluconeogenesis, it could be expected that corticosterone, even though not present in any quantity in the hamster, might, by reason of its steroidal configuration, effect some stimulation. However, it is obvious that, under the experimental conditions adopted, it does not. The data as discussed above confirm the view that the steroidal synthesis and release mechanisms of the hamster differ from those of most animals.

V. CONCLUSIONS.

Some endocrinological responses of the hamster are similar to those of the albino rat; however, there are important differences.

In the hamster, as in the rat, chemical thyroidectomy effects little or no significant change in the ascorbic acid content of the pituitary gland.

The hamster, unlike the rat, shows no significant change in the ascorbic acid content of the adrenal, pituitary, hypothalamus, cerebrum, or liver for a period of up to 15 days following ovariectomy.

l-Alanine does not exert a gluconeogenic effect upon the liver of fasted hamsters of either sex, whereas it rapidly replenishes the glycogen stores of fasted rats. Following adrenalectomy, neither hamsters nor rats show any increase in liver glycogen after having ingested *l*-alanine.

Corticosterone is unable to stimulate repletion of liver glycogen in either the normal or adrenalectomized hamster, whereas the closely allied steroid cortisol is very efficacious under these conditions in the rat.

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UNCLASSIFIED

Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract, and indexing annotation must be entered when the overall report is classified)

| | | | |
|--|------------------------|--|----------------|
| 1. ORIGINATING ACTIVITY (Corporate author) | | 2a. REPORT SECURITY CLASSIFICATION | |
| CO, Edgewood Arsenal ATTN: SMUEA-RMP Edgewood Arsenal, Maryland 21010 | | UNCLASSIFIED | |
| 3. REPORT TITLE | | 2b. GROUP | |
| OBSERVATIONS ON CERTAIN ENDOCRINOLOGICAL RESPONSES OF THE HAMSTER | | NA | |
| 4. DESCRIPTIVE NOTES (Type of report and inclusive dates) | | | |
| This work was started in July 1966 and completed in August 1967. | | | |
| 5. AUTHOR(S) (First name, middle initial, last name) | | | |
| Paul F. Robinson | | | |
| 6. REPORT DATE | 7a. TOTAL NO. OF PAGES | 7b. NO. OF REFS | |
| January 1970 | 29 | 19 | |
| 8a. CONTRACT OR GRANT NO. | | 8b. ORIGINATOR'S REPORT NUMBER(S) | |
| b. PROJECT NO. | | EATR 4328 | |
| c. Task No. IT061101A 0215 | | 8c. OTHER RT NO(S) (Any other numbers that may be assigned this report) | |
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| 11. SUPPLEMENTARY NOTES | | 12. SPONSORING MILITARY ACTIVITY | |
| In-House Laboratory Independent Research - Edgewood | | NA | |
| 13. ABSTRACT | | | |
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| 14. KEYWORDS | | | |
| Hamster | Thyroid | Cerebrum | L-Alanine |
| Rat | Pituitary | Liver | Corticosterone |
| Adrenal | Hypothalamus | Gluconeogenesis | |

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